

**To:** Akihiko Hirose[akihikoh@dranihs.net];  
 rhryuichihasegawa08@gmail.com[rhryuichihasegawa08@gmail.com]; 'Michael L. Caldwell'[MCaldwell@zacfirm.com]; Beck, Nancy[Beck.Nancy@epa.gov]; Birchfield, Norman[Birchfield.Norman@epa.gov]; yamazaki[k-yamazaki@jisha.or.jp];  
 kmdilwali@intsci.com[kmdilwali@intsci.com]; 'Michael L. Caldwell'[MCaldwell@zacfirm.com];  
 Pierre\_Therriault@hc-sc.gc.ca[Pierre\_Therriault@hc-sc.gc.ca]; Richard Charron[Richard.Charron@hc-sc.gc.ca]; Sams, Reeder[Sams.Reeder@epa.gov];  
 mhoneycu@tceq.state.tx.us[mhoneycu@tceq.state.tx.us]; Deshpande, Satish (MOECC)[Satish.Deshpande@ontario.ca]; sarah.labib@canada.ca[sarah.labib@canada.ca]; Shannon Ethridge[sethridg@tceq.state.tx.us]; Barbara Sassi[barbara.sassi@health.mo.gov];  
 dennis.wambuguh@health.mo.gov[dennis.wambuguh@health.mo.gov]; Chris Prucha[cprucha@wm.com]; h-kano@jisha.or.jp[h-kano@jisha.or.jp]; Maier, Michael (maierma)[maierma@ucmail.uc.edu]; t-kasai@jisha.or.jp[t-kasai@jisha.or.jp];  
 sethridg@tceq.state.tx.us[sethridg@tceq.state.tx.us]; Robert Maronpot[maronpot@me.com]; Whalan, John[Whalan.John@epa.gov]; James E. Klaunig[jklauni@indiana.edu]; Jayne Wright[jayne@jaynewright.co.uk]; Nadine Weinberg[nadine.weinberg@erm.com]; Garoutte, Jonathan[Jonathan.Garoutte@health.mo.gov]; flagac@michigan.gov[flagac@michigan.gov];  
 Joseph.Haney@tceq.texas.gov[Joseph.Haney@tceq.texas.gov]; Phelka, Amanda[aphelka@nsf.org]; jenglish@nsf.org[jenglish@nsf.org]; Laessig, Susan[Laessig.Susan@epa.gov]; Herbert, Ron (NIH/NIEHS) [E][herbert@niehs.nih.gov]; oono-yurie@mhlw.go.jp[oono-yurie@mhlw.go.jp];  
 toxpathmcc[toxpathmcc@bellsouth.net]; Jeff.Wenzel@health.mo.gov[Jeff.Wenzel@health.mo.gov]; Maria Hegstad[mhegstad@iwpnews.com]; Doug Wolf[Wolf.Doug@epamail.epa.gov];  
 helen.goeden@state.mn.us[helen.goeden@state.mn.us]; James.kelly@state.mn.us[James.kelly@state.mn.us]; Franz, Christina[Christina\_Franz@americanchemistry.com]; Kylie Brockenfelt[KBrockenfelt@epl-inc.com];  
 riesd@michigan.gov[riesd@michigan.gov]; 'Sager, Shawn'[Shawn.Sager@arcadis.com]; HOWARD, WILLIAM B GS-13 USAF AFMC AFCEC/CZTE[william.howard.40@us.af.mil]; Hamlin, Mel (NIH/NIEHS) [C] (hamlin@niehs.nih.gov)[hamlin@niehs.nih.gov]; ruckner@rx.uga.edu[ruckner@rx.uga.edu]; Harvey Clewell[HCClewell@thehamner.org]; david\_dorman@ncsu.edu[david\_dorman@ncsu.edu];  
 fjmiller@nc.rr.com[fjmiller@nc.rr.com]; rpsharma@uga.edu[rpsharma@uga.edu]; Vandenberg, John[Vandenberg.John@epa.gov]  
**Cc:** Jeri.Higginbotham@ky.gov[Jeri.Higginbotham@ky.gov];  
 jcrum@hampmathews.com[jcrum@hampmathews.com]; burleighflayer@ppg.com[burleighflayer@ppg.com]; Nance, Patricia (nancepm)[nancepm@ucmail.uc.edu];  
 'Forsberg, Norman'[Norman.Forsberg@arcadis.com]; 'Mark Lafronconi'[Mark.Lafronconi@erm.com]; Reichard, John (reichajf)[reichajf@ucmail.uc.edu]  
**From:** Dourson, Michael (doursoml)  
**Sent:** Mon 6/5/2017 10:08:41 PM  
**Subject:** In Print---1,4-Dioxane Publication

Dear Colleagues

On behalf of the authors, I am pleased to let you know that our publication is now in print as shown below. The paper was developed under the umbrella of the Alliance for Risk Assessment (ARA), and is open access thanks to Norm Forsberg and his company Arcadis. Please feel free to share this paper as needed.

Cheers!

Michael Dourson

— Risk Science Center (formerly TERA Center) sponsors the International Toxicity Estimates for Risk (ITER) database of risk assessment values on Toxnet: <http://toxnet.nlm.nih.gov/>



**From:** RSS Feed via IFTTT <[weeklydigest@ifttt.com](mailto:weeklydigest@ifttt.com)>

**Date:** Monday, June 5, 2017 at 8:14 AM

**To:** Michael Dourson <[doursoml@ucmail.uc.edu](mailto:doursoml@ucmail.uc.edu)>

**Subject:** Weekly Digest: If new feed item from <http://rss.sciencedirect.com/publication/science/02732300>, then add to weekly digest sent to [michael.dourson@uc.edu](mailto:michael.dourson@uc.edu) on (7 items)

## **Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1,4-dioxane**

Publication date: August 2017

**Source:** Regulatory Toxicology and Pharmacology, Volume 88

**Author(s):** Michael L. Dourson, Jeri Higginbotham, Jeff Crum, Heather Burleigh-Flayer, Patricia Nance, Norman D. Forsberg, Mark Lafranconi, John Reichard

Previous work has shown that the weight of evidence supports the hypothesis that 1,4-dioxane causes liver tumors in rodents through cytotoxicity and subsequent regenerative hyperplasia. Questions regarding a lack of concordant findings for this mode of action (MOA) in mice have not been resolved, however. In the current work, a reanalysis of data from two chronic mouse cancer bioassays on 1,4-dioxane, one 13-week mouse study, seven rat cancer bioassays, coupled with other data such as 1,4-dioxane's negative mutagenicity, its lack of up-regulated DNA repair, and the appearance of liver tumors with a high background incidence, support the conclusion that rodent liver tumors, including those in mice, are evoked by a regenerative hyperplasia MOA. The initiating event for this MOA is metabolic saturation of 1,4-dioxane. Above metabolic saturation, higher doses of the parent compound cause an ever increasing toxicity in the rodent liver as evidenced by higher blood levels of enzymes indicative of liver cell damage and associated histopathology that occurs in a dose and time related manner. Importantly, alternative modes of action can be excluded. The observed liver toxicity has a threshold in the dose scale at or below levels that saturate metabolism, and generally in the range of 9.6–42 mg/kg-day for rats and 57 to 66 mg/kg-day for mice. It follows that threshold approaches to the assessment of this chemical's toxicity are

supported by the non-mutagenic, metabolic saturation kinetics, and cytotoxicity-generated regenerative repair information available for 1,4-dioxane promoted rodent liver tumors.

via ScienceDirect Publication: Regulatory Toxicology and Pharmacology <http://ift.tt/2r6ix2E> May 30, 2017 at 02:02AM

via RSS

Feed <http://rss.sciencedirect.com/action/redirectFile?&zone=main&Activity=feed&usageTy>

**From:** Michael Dourson <doursoml@ucmail.uc.edu>

**Date:** Thursday, February 23, 2017 at 2:28 PM

**To:** Akihiko Hirose <akihikoh@dranihs.net>, "rhryuichihasegawa08@gmail.com" <rhryuichihasegawa08@gmail.com>, "Michael L. Caldwell" <MCaldwell@zacfirm.com>, "Beck, Nancy" <Nancy\_Beck@americanchemistry.com>, "Birchfield, Norman" <Birchfield.Norman@epa.gov>, yamazaki <k-yamazaki@jisha.or.jp>, "kmdilwali@intsci.com" <kmdilwali@intsci.com>, "Michael L. Caldwell" <MCaldwell@zacfirm.com>, "Pierre Therriault@hc-sc.gc.ca" <Pierre\_Therriault@hc-sc.gc.ca>, Richard Charron <Richard.Charron@hc-sc.gc.ca>, "Sams, Reeder" <Sams.Reeder@epa.gov>, Michael Honeycutt <MHoneycu@tceq.state.tx.us>, "Deshpande, Satish (MOECC)" <Satish.Deshpande@ontario.ca>, "Labib, Sarah (HC/SC)" <sarah.labib@canada.ca>, Shannon Ethridge <sethridg@tceq.state.tx.us>, Barbara Sassi <barbara.sassi@health.mo.gov>, Dennis Wambuguh <dennis.wambuguh@health.mo.gov>, Chris Prucha <cprucha@wm.com>, "h-kano@jisha.or.jp" <h-kano@jisha.or.jp>, Andy Maier <maierma@ucmail.uc.edu>, "t-kasai@jisha.or.jp" <t-kasai@jisha.or.jp>, "sethridg@tceq.state.tx.us" <sethridg@tceq.state.tx.us>, Robert Maronpot <maronpot@me.com>, "Whalan, John" <Whalan.John@epa.gov>, "Klaunig, James E." <jklauni@indiana.edu>, Jayne Wright <jayne@jaynewright.co.uk>, Nadine Weinberg <nadine.weinberg@erm.com>, "Garoutte, Jonathan" <Jonathan.Garoutte@health.mo.gov>, "Flaga, Christine (DEQ)" <FLAGAC@michigan.gov>, "Joseph.Haney@tceq.texas.gov" <Joseph.Haney@tceq.texas.gov>, "Phelka, Amanda" <aphelka@nsf.org>, "English, Joanne Caroline" <jenglish@nsf.org>, "Laessig, Susan" <Laessig.Susan@epa.gov>, "Herbert, Ron (NIH/NIEHS) [E]" <herbert@niehs.nih.gov>, "oono-yurie@mhlw.go.jp" <oono-yurie@mhlw.go.jp>, toxpathmcc <toxpathmcc@bellsouth.net>, "Jeff.Wenzel@health.mo.gov" <Jeff.Wenzel@health.mo.gov>, Maria Hegstad <mhegstad@iwpnews.com>, Doug Wolf <Wolf.Doug@epamail.epa.gov>, "Goeden, Helen (MDH)" <Helen.Goeden@state.mn.us>, "Kelly, James (MDH)" <james.kelly@state.mn.us>, "Franz, Christina" <Christina\_Franz@americanchemistry.com>, Kylie Brockenfelt <KBrockenfelt@epl-inc.com>, "Ries, Divinia (DEQ)" <RIESD@michigan.gov>, "Sager, Shawn" <Shawn.Sager@arcadis.com>, "HOWARD, WILLIAM B GS-13 USAF AFMC AFCEC/CZTE" <william.howard.40@us.af.mil>, "Hamlin, Mel (NIH/NIEHS) [C]" <hamlin@niehs.nih.gov> <hamlin@niehs.nih.gov>, "ruckner@rx.uga.edu" <ruckner@rx.uga.edu>, Harvey Clewell <HClewell@thehamner.org>, "david\_dorman@ncsu.edu" <david\_dorman@ncsu.edu>, "fjmiller@nc.rr.com" <fjmiller@nc.rr.com>, "rpsharma@uga.edu" <rpsharma@uga.edu>, John Vandenberg <Vandenberg.John@epamail.epa.gov>

**Cc:** "Higginbotham, Jeri" (EEC) <Jeri.Higginbotham@ky.gov>, "jcrum@hampmathews.com" <jcrum@hampmathews.com>, "Burleigh-Flayer, Heather" <burleighflayer@ppg.com>, Patricia Nance

<nancepm@ucmail.uc.edu>, "'Forsberg, Norman'" <Norman.Forsberg@arcadis.com>, 'Mark Lafranconi'  
<Mark.Lafranconi@erm.com>

**Subject:** Accepted 1,4-Dioxane Publication

Dear Colleagues

On behalf of the authors listed in the CC section of this email, it gives me great pleasure to state that a manuscript entitled "Update: Mode of Action (MOA) for Liver Tumors Induced by Oral Exposure to 1,4-Dioxane" has been accepted by Regulatory Toxicology and Pharmacology. An abstract is found below.

This work was conducted under the auspices of the Alliance for Risk Assessment (ARA), and involved multiple groups acting collaboratively. Updates of this accepted text prior to it being published will be posted on the Alliance for Risk Assessment (ARA) website, specifically, <http://allianceforrisk.org/14-dioxane-analysis>.

Please feel free to let your colleagues know as well.

Sincerely,



Michael L. Dourson, Ph.D., DABT, FATS, FSRA  
Professor  
Risk Science Center (formerly TERA)  
Department of Environmental Health  
University of Cincinnati, College of Medicine  
160 Panzeca Way  
Cincinnati OH 45267-0056

[michael.dourson@uc.edu](mailto:michael.dourson@uc.edu)  
513-558-7949  
419-892-2502 (Mondays)  
<http://eh.uc.edu/tera/>



## Abstract

Previous scientific studies show that the weight of evidence supports the hypothesis that 1,4-dioxane causes liver tumors in rodents through cytotoxicity and subsequent regenerative

hyperplasia. Questions regarding a lack of concordant findings for this mode of action (MOA) in mice have not been resolved, however. In the current work, a reanalysis of data from two chronic mouse cancer bioassays on 1,4-dioxane, one 13-week mouse study, seven rat cancer bioassays, coupled with other data demonstrating negative mutagenicity, lack of up-regulated DNA repair, and the appearance of liver tumors with a high background incidence, support the conclusion that rodent liver tumors, including those in mice, are evoked by a regenerative hyperplasia MOA. The initiating event for this MOA is metabolic saturation of 1,4-dioxane. Above metabolic saturation, higher doses of the parent compound cause an ever increasing toxicity in the rodent liver as evidenced by higher blood levels of enzymes indicative of liver cell damage and associated histopathology that occurs in a dose and time related manner. Importantly, alternative modes of action can be excluded. The observed liver toxicity has a threshold in the dose scale at or below levels that saturate metabolism, and generally in the range of 9.6 to 42 mg/kg-day for rats and 57 to 66 mg/kg-day for mice. It follows that threshold approaches to the assessment of this chemical's toxicity are supported by the non-mutagenic, metabolic saturation kinetics, and cytotoxicity-generated regenerative repair information available for 1,4-dioxane promoted rodent liver tumors.

**From:** [eesserver@eesmail.elsevier.com](mailto:eesserver@eesmail.elsevier.com) [<mailto:eesserver@eesmail.elsevier.com>]  
**Sent:** Thursday, February 23, 2017 10:33 AM  
**To:** Nance, Patricia (nancepm) <[nancepm@ucmail.uc.edu](mailto:nancepm@ucmail.uc.edu)>; [pnance1972@gmail.com](mailto:pnance1972@gmail.com)  
**Subject:** RTP-16-335R2: Final Decision

Ms. No.: RTP-16-335R2

Title: Update: Mode of Action (MOA) for Liver Tumors Induced by Oral Exposure to 1,4-Dioxane

Corresponding Author: Ms. Patricia Nance

Authors: Michael Dourson; Jeri Higginbotham; Jeff Crum; Heather Burleigh-Flayer; Norman Forsberg; Mark Lafranconi

Dear Ms. Nance,

Congratulations. I am pleased to inform you that your manuscript, referenced above, has been accepted for publication in Regulatory Toxicology and Pharmacology.

Many thanks for this paper. We look forward to the submission of your future manuscripts to Regulatory Toxicology and Pharmacology.

Your accepted manuscript will now be transferred to our production department and work will begin on creation of the proof. If we need any additional information to create the proof, we will let you know. If not, you will be contacted again in the next few days with a request to approve the proof and to complete a number of online forms that are required for publication.

When your paper is published on ScienceDirect, you want to make sure it gets the attention it deserves. To help you get your message across, Elsevier has developed a new, free service called AudioSlides: brief, webcast-style presentations that are shown (publicly available) next to your published article. This format gives you the opportunity to explain your research in your own words and attract interest. You will receive an invitation email to create an AudioSlides presentation shortly. For more information and examples, please visit <http://www.elsevier.com/audioslides>.

With kind regards,

Dr. Gio Batta Gori, Editor-in-Chief  
Regulatory Toxicology and Pharmacology  
E-mail: [rtp@elsevier.com](mailto:rtp@elsevier.com)